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The Root Cause of Post-traumatic and Developmental Stress Disorder

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14. ABSTRACT

Our overarching scientific hypothesis holds that serotonergic influences on brain development driven by genetics and early experience induce a variation of normal brain anatomy that makes the brain highly susceptible to the effects of severe stress. We are studying this question using both clinical and basic approaches. New findings from our lab funded by VA support the existence of an anatomical phenotype conferring susceptibility to depression, and the current work seeks to extend these findings to PTSD. After TATRC review in January of 2011, a revised research plan was developed to include a pre/post-deployment study at Fort Hood and anatomical studies of PTSD in collaboration with NIMH, Yale and USUHS. The revised budget was resubmitted in July and we are awaiting release of funds from contracting to begin the work. Post-mortem brain tissue from 9 brains have been sent to NIMH for a gene expression/transcriptome study to investigate RNA expression. This tissue has been combined with 6 PTSD brains from the NIMH Clinical Brain Disorder Branch whose clinical diagnosis are being verified as consistent with our diagnostic methods. Golgi methods for analysis of prefrontal anatomy have been developed at Yale and we are awaiting contracting to execute the subcontract. The clinical protocol for the pre/post-deployment study at Fort Hood is under review at BAMC IRB and a revised CRADA is being prepared.

15. SUBJECT TERMS
None provided

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INTRODUCTION:

Our overarching scientific hypothesis holds that serotonergic influences on brain development driven by genetics and early experience induce a variation of normal brain anatomy that makes the brain highly susceptible to the effects of severe stress. The new goal of Project 1 is to describe the progression of post-deployment stress disorders (PTSD, major depression, suicidality) in active duty troops using predeployment/postdeployment structured clinical interviews, and to investigate developmental and environmental factors that influence predisposition to PTSD and depression. A subset of participants will be selected to have predeployment/postdeployment MRI and psychophysiological analysis. Using DNA gathered from clinical trials, we will investigate genetic factors influencing resiliency and susceptibility to stress disorders using a panel of 20 genes that we have tested and validated. Project 2 will investigate post-mortem anatomy in subjects with major depression and/or PTSD. Both molecular and histological techniques will be employed to study the brains already collected. An overarching goal of the Program is integration of data across the projects to compare and contrast the potential for different assessment paradigms (MRI anatomy, fMRI, evoked potentials, startle, genetic profiling) to screen for resiliency and predisposition to post-traumatic and developmental stress disorder stress disorders.

BODY:

KEY RESEARCH ACCOMPLISHMENTS:

Administrative:

Approval to move forward with the redesigned Project 1 was received from TATRC and MOMRP in March, 2011 and the redesigned budget was submitted in July 2011. We are currently awaiting release of funding to begin the work. The IRB for Project 1 was submitted to BAMC in February, 2012.

Project Specific:

Project 1:

Task 1: Sample 2000 active duty/guard troops pre-deployment

a. Diagnostic interview (SCID)
b. Depression symptoms
c. Stress battery (DRRI, development history, suicidality)
d. Blood for DNA/RNA
e. Medical testing (CBC/TSH/CMP)

Task 2: Resample/test post-deployment

Progress 04/29/12

IRB approval is pending at BAMC. We are awaiting release of funding to begin hiring for this project. One SCID trainer has completed training and is awaiting hiring to begin training other interviewers. Ten candidates have been interviewed and are awaiting release of funding to hire 5-6 of these. All study documents are prepared.

Project 2 Neurobiology

Task 1: Pre-deployment/post-deployment MRI testing *300 scanning sessions*

Progress 04/29/12

IRB approval for MRI work is pending at BAMC. We are awaiting release of funding to begin hiring for this project. All study documents are prepared.

Task 2. Continue collection of PTSD, MDD and control brains

Progress 04/29/12

2 additional PTSD and 2 controls have been collected in 2011. In addition, 3 MDD brains were collected. Two of these brains have completed post-mortem diagnosis and contributed samples for the PTSD gene expression study.

Task 3. Compare gene expression in the frontal cortex of PTSD and controls.

Progress 04/29/12

A consortium was established with NIMH Clinical Brain Disorders Branch to study frontal cortical gene expression in PTSD vs controls. 9 PTSD brains from our collection and 6 PTSD brains from NIMH will be used in the study. This is the largest post-mortem PTSDcohort ever studied. Frontal cortical tissue(area 9/25) has been sent to NIMH for analysis, including DNA microarray, RNA expression (microarray) and confirmatory RNA expression (RNAseq).

Task 4. Compare anatomical markers in frontal cortex/hippocampus of PTSD, MDD and controls, with 5HTTLPR and other genetic variants as cofactors.

Progress 04/29/12

A collaboration with Yale Neurobiology was formed to study frontal cortical pyramidal cell morphology in PTSD vs controls. 9 PTSD brains from our collection and 6 PTSD brains from NIMH will be used in the study. Test frontal cortical tissue has been sent to Yale for validation of the golgi technique in fixed tissue.

Of the 5 procedures tested, rapid golgi was determined to be the most effective. Initiation of work on this task awaits release of funding.

REPORTABLE OUTCOMES: None
CONCLUSION: No scientific conclusions have been made at this point in time.
APPENDICES: None.